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BACKGROUND

Worldwide, lung cancer is the most commonly diagnosed cancer and causes more deaths than any other cancer *[1,2]*. Its high mortality rate results from both a high incidence rate and a low survival rate, with only 14% of US lung cancer patients surviving 5 years after diagnosis *[3]*. Lung cancer is also the leading cause of cancer death in most countries *[4-6]*.

International variations in the incidence of lung cancer are striking, with age-standardized incidence rates (ASRs) per 100,000 below 10 in parts of Africa, China, and South America, and over 100 in some Black populations in the United States *[2,5]*.

Throughout all age groups, incidence of lung cancer rises sharply with age *[4]*. This pattern is sometimes complicated by cohort effects related to changes in tobacco consumption *[7-9]*.

Tobacco use is by far the most important risk factor in the development of lung cancer. In 1979, the US Surgeon General estimated that 90% of lung cancer deaths in males and 79% in females were due to cigarette smoking *[4]*. Smoking more than 20 cigarettes a day has been shown to confer a risk of between 15- and 25-fold relative to nonsmokers *[10-12]*. Both the duration and intensity of cigarette smoking increases the risk, as does the tar content and the lack of a filter *[13]*. The risk decreases with time after smoking cessation, with long-term ex-smokers approaching but not reaching the risk of nonsmokers *[14]*. Other types of tobacco smoking, such as pipe, cigar, and water-pipe smoking, are also linked to lung cancer, although the relative risks are not as high as for cigarette smoking *[4]*. Exposure to other persons' cigarette smoke (known as passive smoking or environmental tobacco smoke) is also related to an increased risk of lung cancer, although the relative risk is understandably much lower than in smokers.

Worldwide, the incidence of lung cancer among males is much higher than among females, due primarily to the lower prevalence of smoking among females. The sex difference in cigarette consumption has diminished, and in many countries lung cancer rates continue to increase among females.

Smoking is related to all the major types of lung cancer, including squamous cell carcinoma, small cell carcinoma, and adenocarcinoma. It used to be thought that adenocarcinoma was not caused by smoking, but in the United States, adenocarcinoma is now the most common type of lung cancer in smokers *[15]*.

Several other risk factors for lung cancer have been identified. Occupational exposures that increase the risk of lung cancer include asbestos *[16]*, which also causes an increase in the risk of mesothelioma, a cancer of the pleura *[17]*. Asbestos exposure and cigarette smoking act synergistically, together raising the risk of lung cancer multiplicatively *[18]*.

Other occupational exposures related to lung cancer include arsenic *[19]*, chromium *[20]*, polycyclic aromatic hydrocarbons *[21]*, and radon. The latter exposure was first discovered among underground miners in North America, Europe, and Asia *[22]*, but is now the source of concern for the general population because many household basements show relatively high levels of radon. It is estimated that in the United States, indoor radon may be the second most important risk factor for lung cancer after cigarette smoking *[23]*. Lung cancer is also one of the major effects of exposure to high doses of ionizing radiation, such as in medical and atomic radiation. Various pollutants in urban air are implicated in lung cancer incidence rates worldwide *[4]*.

Epidemiological investigations have shown associations between consumption of fresh vegetables and fruits and a low risk of lung cancer *[24]*. Investigations have focused on carotenoid intake and serum carotenoid levels *[4]*, both of which have also shown associations with low risk of lung cancer. However, several randomized trials of beta-carotene supplementation have yielded the unexpected result that among smokers, high doses of beta-carotene can increase the risk of lung cancer *[25,26]*. The biological explanation is as yet unclear.

There has been some evidence of lung cancer clustering in families, with suggestions that heritable factors may also play a part in lung cancer etiology *[4]*. Much effort has gone into discovering genetic susceptibility factors, and the P450 gene *CYP2D6*, which regulates debrisoquine metabolism, was at one time thought to be important, but later results have indicated that at most its effect is modest *[27]*. Reduced activity of glutathione S-transferase (GST) has also been linked to increased risk of lung cancer, and *GSTM1* deficiency is associated with a moderately elevated relative risk *[28]*.

RESULTS

Table 6.1 presents the total numbers and proportions by age group, incidence rates age-standardized to the world standard, and age- and sex-specific incidence rates for MECC populations and the US SEER population.

The total numbers of cases from each population were at least a few hundred, except for Cypriot, Egyptian, and Israeli Arab females. The proportions of cases over 70 years of age were around 50% in the US SEER and Israeli Jewish populations, 40% in Cypriots, and 20%-30% in Egyptians, Jordanians, and Israeli Arabs. These differences are largely due to differences in the population age distribution (Table 6.1).

The overall ASRs were much lower in the MECC populations than in US SEER. The rates in Israel (Jews and Arabs) were approximately half that of US SEER. In Cyprus, Jordan, and Egypt, rates were between one-third and one-fifth of the US SEER rate (Table 6.1).

Among males, the lung cancer ASR in MECC populations was highest in Israeli Arabs, followed by Israeli Jews, Cypriots, Jordanians, and Egyptians. The rate among Israeli Arab males was 34% higher than in Israeli Jewish males (Table 6.1).

Worldwide statistics *[2]* show that the lung cancer ASRs for males in other Middle Eastern populations, such as Algeria (17.1) and Kuwait (20.0), were close to that in Jordan (16.4), while the rate in other Western countries, such as Canada (59.0) and Ireland (42.3), were similar to that in the United States.

The lung cancer incidence rates in females were lower than in males. All the MECC female populations displayed rates far lower than in the US SEER female population. Among the MECC female populations, the highest rate was in Israeli Jews, but this was only one-third the rate in US SEER. All of the other MECC populations had rates less than half that of Israeli Jews, with Jordanians and Egyptians having the lowest rates. It is notable that the rate among Israeli Arab females was not much higher than the rates among Jordanian and Egyptian females, a reflection of the similarities in cultures and habits related to smoking among females in these 3 Arab populations. The female ASRs in Algerians (1.9) and Omanians (2.6) *[4]* were somewhat lower than in Jordanians (3.1), Egyptians (3.7), and Israeli Arabs (4.8), but Kuwaitis (5.3) had a slightly higher rate.

Table 6.1 also presents the age- and sex-specific incidence rates in 4 broad age groups. As expected, the rates increased with age, from the youngest age group (<50 years of age) to the oldest (age 70 years and older). One interesting aspect of the age-specific incidence rates is that the ratio of the MECC population rates to the US SEER rates decreased with age. For example, the ratios of the rates in male Israeli Jews to those in the male US SEER population were 0.85 for <50 years of age, 0.64 for 50-60 years of age, 0.61 for 60-70 years of age, and 0.50 for age 70 years and older. For male Israeli Arabs, the ratios were 1.09 for <50 years of age, 1.08 for 50-60 years of age, 0.79 for 60-70 years of age, and 0.62 for age 70 years and older.

Such decreasing ratios are suggestive (but not conclusive) evidence of a cohort effect. It is possible that more recent generations in the Middle East have increasingly taken up cigarette smoking, which has caused the younger age groups to have lung cancer rates more like those seen in the US population. Unfortunately, there is little information about the history of smoking prevalence in the MECC populations, except for that in Israeli Jews. Figure 6.1 shows smoking prevalence from 1965 to 2000 in Israeli Jewish and US males, as well as the lung cancer ASRs in both populations from the mid-1970s onwards. It appears that in the latter part of the 1960s, approximately 30 years before the period covered by this monograph, the smoking prevalence in Israel was not very much lower than in the United States, and that by 1973, 25 years before the monograph's period, the smoking prevalence in Israel had surpassed that in the United States. Thus, although Figure 6.1 does indeed indicate that recent generations of males in Israel have smoked as much or more than their counterparts in the United States, the similarity of the smoking prevalence 25-30 years before this monograph's timeframe raises the question why Israeli rates of lung cancer are not already much closer to those of the United States. While further analysis is required, including an examination of past

Table 6.1. Lung Cancer: Number of Cases, Age Distribution, and Age-Standardized Incidence Rates, by Age and Sex, in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER − 1996-2001*

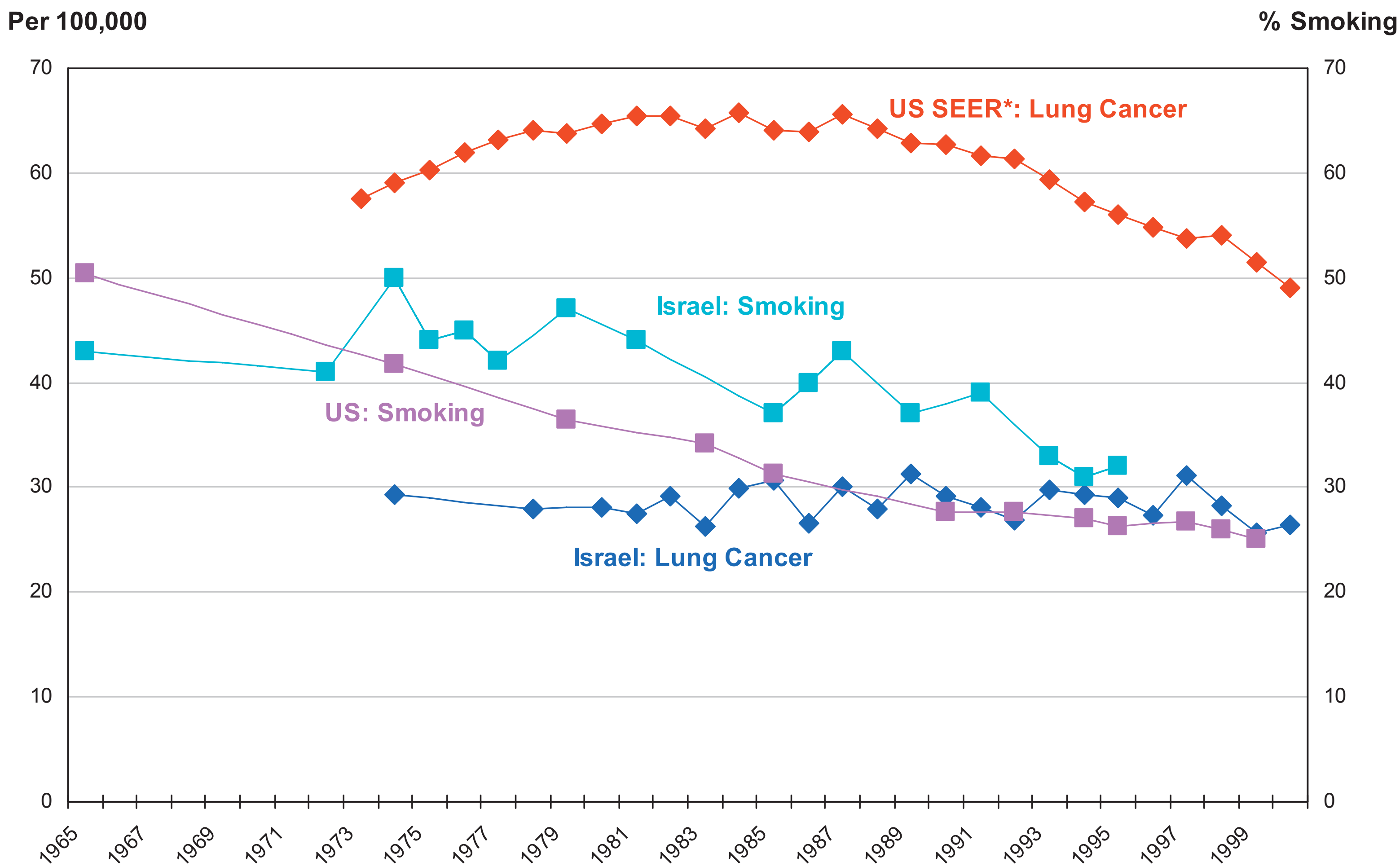
	Cyprus 1998-2001			Israel (Jews) 1996-2001			Israel (Arabs) 1996-2001			Egypt 1999-2001			Jordan 1996-2001			US SEER† 1999-2001		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Total cases	514	423	91	7,402	4,892	2,510	706	611	95	496	370	126	1,336	1,128	208	63,559	34,973	28,586
Age Groups (Distribution)																		
<50	8.4%	6.9%	*15.4%*	7.6%	6.9%	8.9%	13.5%	11.6%	25.3%	19.6%	16.2%	29.4%	15.3%	13.8%	23.1%	5.7%	5.5%	5.9%
50-59	19.1%	19.1%	18.7%	13.8%	13.5%	14.3%	24.5%	26.5%	*11.6%*	22.2%	22.7%	20.6%	26.0%	26.5%	23.1%	14.7%	14.9%	14.4%
60-69	31.7%	32.2%	29.7%	29.6%	31.9%	25.1%	31.7%	32.9%	24.2%	36.5%	39.5%	27.8%	37.0%	37.6%	33.7%	26.8%	27.7%	25.8%
70+	40.9%	41.8%	36.3%	49.1%	47.7%	51.7%	30.3%	29.0%	38.9%	21.8%	21.6%	22.2%	21.8%	22.1%	20.2%	52.8%	51.9%	54.0%
Age Groups (Rates)‡																		
Total rate	13.4	23.4	4.7	19.0	28.4	11.4	20.4	38.0	4.8	7.7	11.9	3.7	9.9	16.4	3.1	39.2	48.6	31.9
<50	1.7	2.3	*1.1*	2.3	2.8	1.8	2.3	3.6	1.0	1.3	1.6	1.0	1.4	2.1	0.6	3.1	3.3	2.9
50-59	32.0	53.4	11.1	40.4	55.1	27.0	49.7	92.9	*6.3*	17.7	26.6	8.4	23.7	39.2	6.9	75.1	86.2	64.5
60-69	75.0	132.2	24.2	105.0	165.5	55.1	109.8	213.2	21.0	42.9	70.9	16.1	59.5	95.7	18.1	223.3	271.1	181.1
70+	97.4	187.6	27.0	155.1	239.9	93.6	159.9	297.2	49.7	52.3	83.1	25.2	61.6	110.7	17.1	359.3	479.9	277.6

The symbols "-" = 1-2 cases; and "[numeral]*" (italic) = 0 or 3-15 cases.

†SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

‡Rates are per 100,000 and are age-standardized to the World Standard Million.

Figure 6.1. Lung Cancer: Age-Standardized Incidence Rates and Smoking Prevalence among Israeli and US White Males – 1965-2000



*SEER 13 Registries, Public Use Data Set, from data submitted November 2004.
Source: Reproduced with permission of Dr. Gad Rennert, who compiled the data from a variety of sources.

age-specific smoking prevalence and age-specific lung cancer rates, it is possible that genetic factors may explain some of the current differences between Israeli and US SEER rates.

The histological type of lung cancer is an important factor in the epidemiology, treatment, and prognosis of lung cancers. Table 6.2 shows data on the histology of lung and pleural cancers in the MECC and US SEER populations.

The percentage of microscopically confirmed cases varied widely among the registries, with a very high rate in Jordan (97.2%), a rate of around 90% in Cyprus and US SEER registries, and lower rates in Israel and Egypt. The high rate in Jordan indicates possible under-diagnosis of lung cancer in that country, whereas the low rates in Israel indicate that the registry may sometimes be missing details of diagnosis in the information provided by the hospitals. The low rate in Egypt may arise from patterns of care of the elderly population there.

Table 6.2 also indicates a remarkably high proportion of adenocarcinoma in the Cyprus population (54.4%), and a similarly remarkable proportion of large cell carcinoma in Egypt (25.6%). These findings, if confirmed, may provide new clues to the etiology of lung cancer.

Table 6.2. Lung Cancer: Number of Cases and Proportions of Microscopic Confirmation and Histologic Type, by Sex, in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER − 1996-2001*

	Cyprus 1998-2001			Israel (Jews) 1996-2001			Israel (Arabs) 1996-2001			Egypt 1999-2001			Jordan 1996-2001			US SEER† 1999-2001		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Total cases microscopically confirmed	467	381	86	5,936	3,950	1,986	594	523	71	383	288	95	1,298	1,095	203	57,126	31,672	25,454
Microscopically confirmed	90.9%	90.1%	94.5%	80.2%	80.7%	79.1%	84.1%	85.6%	74.7%	77.2%	77.8%	75.4%	97.2%	97.1%	97.6%	89.9%	90.6%	89.0%
Distribution of Microscopically Confirmed Cases																		
Histologic distribution‡	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Carcinoma	95.3%	94.8%	97.7%	96.3%	96.4%	96.1%	95.0%	95.2%	93.0%	94.8%	94.4%	95.8%	96.7%	96.9%	95.6%	98.8%	98.8%	98.8%
Squamous cell carcinoma	24.6%	27.0%	*14.0%*	24.8%	29.7%	15.0%	29.0%	31.4%	*11.3%*	21.1%	25.3%	*8.4%*	31.4%	33.9%	17.7%	21.0%	24.8%	16.3%
Adenocarcinoma	54.4%	49.1%	77.9%	36.6%	30.9%	47.8%	31.0%	28.5%	49.3%	29.5%	23.3%	48.4%	27.7%	24.7%	43.4%	37.2%	34.2%	40.9%
Small cell carcinoma	8.1%	9.4%	-	9.6%	10.8%	7.3%	14.8%	14.3%	*18.3%*	13.3%	15.3%	*7.4%*	13.4%	14.3%	8.4%	14.1%	13.1%	15.3%
Large cell carcinoma	*2.1%*	*2.4%*	-	3.9%	4.3%	3.1%	3.2%	3.6%	*0.0%*	25.6%	26.4%	23.2%	3.5%	3.5%	*3.9%*	6.2%	6.4%	5.9%
Other specified carcinomas	3.4%	*3.7%*	-	16.9%	16.0%	18.7%	13.0%	12.8%	*14.1%*	*2.4%*	*2.8%*	-	4.9%	4.6%	*6.9%*	8.3%	8.1%	8.6%
Unspecified carcinoma	*2.6%*	*3.2%*	*0.0%*	4.5%	4.7%	4.2%	4.0%	4.6%	*0.0%*	*2.9%*	*1.4%*	*7.4%*	15.8%	15.9%	15.3%	12.1%	12.3%	11.8%
Sarcoma	-	-	*0.0%*	0.5%	0.5%	*0.6%*	-	*0.0%*	-	*0.0%*	*0.0%*	*0%*	*0.4%*	*0.0%*	*2.5%*	0.2%	0.2%	0.2%
Mesothelioma	-	-	*0.0%*	0.3%	0.4%	*0.2%*	-	-	*0.0%*	-	-	*0.0%*	*0.3%*	*0.4%*	*0.0%*	0.1%	0.1%	*0.0%*
Unspecified cancer	4.1%	4.5%	-	2.5%	2.4%	2.8%	3.7%	4.0%	-	5.0%	*5.2%*	*4.2%*	2.3%	2.5%	*1.5%*	0.8%	0.8%	0.8%
Other specified types	*0.0%*	*0.0%*	*0.0%*	0.3%	*0.3%*	*0.4%*	*0.7%*	-	-	*0.0%*	*0.0%*	*0.0%*	*0.3%*	*0.3%*	-	0.2%	0.2%	0.2%

The symbols "-" = 1-2 cases; and "[numeral]*" (italic) = 0 or 3-15 cases.

†SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

‡Percentages should sum over a column to 100% (with some rounding). However, where a percentage has been suppressed because it is based on only 1 or 2 cases, the remaining percentages will not sum to 100%.

SUMMARY AND CONCLUSIONS

The data show that lung cancer incidence in the MECC populations was much lower than in the US SEER population. However, the younger age groups (under 60 years of age) in the Israeli Arab male population had rates comparable to those in US SEER, and it is possible that a cohort effect is in progress, whereby rates in the older age groups will also reach or surpass those in the United States. There is also a hint of a similar phenomenon among the Israeli Jewish male population, although from past smoking prevalence data one might expect to see higher rates than are currently being observed. It is possible that genetic factors may explain part of the difference currently seen between Israeli Jewish and US SEER rates. Apart from the Israeli Arabs, other Arab populations in MECC appear to have had low rates, although reports of higher smoking prevalence in these populations give reason for greater vigilance.

Unusual histological patterns in Cyprus, with a high proportion of adenocarcinoma, and in Egypt, with a high proportion of large cell carcinoma, deserve further examination.

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